PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

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WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	27 OCT 2004
Applicant's or agent's file reference 1789-12401	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US04/07600	12 March 2004 (12.03.2004)	13 March 2003 (13.03.2003)

International Patent Classification (IPC) or both national classification and IPC

IPC(7): A 61 F 002/02 and US Cl.: 623/11.11, 1, 11, 12, 66 ; 424/ 422-428; 428/304.4, 311.51.

Applicant

WILLIAM MARSH RICE UNIVERSITY

1. This opinion contains indications relating to the following items:

- ☒ Box No. I — Basis of the opinion
- ☐ Box No. II — Priority
- ☐ Box No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV — Lack of unity of invention
- ☒ Box No. V — Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI — Certain documents cited
- ☐ Box No. VII — Certain defects in the international application
- ☐ Box No. VIII — Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis(b)* that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/ US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer Ms. Arti Singh Telephone No. 571-272-0944

Form PCT/ISA/237 (cover sheet) (January 2004)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US04/07600

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material

      ☐ in written format

      ☐ in computer readable form

   c. time of filing/furnishing

      ☐ contained in international application as filed.

      ☐ filed together with the international application in computer readable form.

      ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US04/07600

Box No. V Reasoned statement under Rule 43 *bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 1-49	YES
	Claims NONE	NO
Inventive step (IS)	Claims NONE	YES
	Claims 1-49	NO
Industrial applicability (IA)	Claims 1-49	YES
	Claims NONE	NO

2. Citations and explanations:

Please See Continuation Sheet

Supplemental Box
In case the space in any of the preceding boxes is not sufficient.

V. 2. Citations and Explanations:

Claims 1-49 lack an inventive step under PCT Article 33(3) as being obvious over USPN 5855610 issued to Vacanti et al. Vacanti et al disclose improved yields of engineered tissue following implantation, and engineered tissue having enhanced mechanical strength and flexibility or pliability, can be obtained by implantation, preferably subcutaneously, of a fibrous polymeric matrix for a period of time sufficient to obtain ingrowth of fibrous tissue and/or blood vessels, which is the removed for subsequent implantation at the site where the implant is desired. The matrix is optionally seeded prior to the first implantation, after ingrowth of the fibrous tissue, or at the time of reimplantation. The time required for fibrous ingrowth typically ranges from days to weeks. The method is particularly useful in making valves and tubular structures, especially heart valves and blood vessels (abstract). The synthetic matrix serves several purposes. It functions as a cell delivery system that enables the organized transplantation of large numbers of cells into the body. The matrix acts as a scaffold providing three-dimensional space for cell growth. The matrix functions as a template providing structural cues for tissue development. In the case of tissues have specific requirements for structure and mechanical strength, the polymer temporarily provides the biomechanical properties of the final construct, giving the cells time to lay down their own extracellular matrix which ultimately is responsible for the biomechanical profile of the construct. The scaffold also determines the limits of tissue growth and thereby determines the ultimate shape of tissue engineered construct. Cells implanted on a matrix proliferate only to the edges of the matrix; not beyond. As previously described, for a tissue to be constructed, successfully implanted, and function, the matrices must have sufficient surface area and exposure to nutrients such that cellular growth and differentiation can occur prior to the ingrowth of blood vessels following implantation. This is not a limiting feature where the matrix is implanted and ingrowth of tissue from the body occurs, prior to seeding of the matrix with dissociated cells. The organization of the tissue may be regulated by the microstructure of the matrix. Specific pore sizes and structures may be utilized to control the pattern and extent of fibrovascular tissue ingrowth from the host, as well as the organization of the implanted cells. The surface geometry and chemistry of the matrix may be regulated to control the adhesion, organization, and function of implanted cells or host cells. In the preferred embodiment, the matrix is formed of polymers having a fibrous structure which has sufficient interstitial spacing to allow for free diffusion of nutrients and gases to cells attached to the matrix surface. This spacing is typically in the range of

Supplemental Box
In case the space in any of the preceding boxes is not sufficient.

100 to 300 microns, although closer spacings can be used if the matrix is implanted, blood vessels allowed to infiltrate the matrix, then the cells are seeded into the matrix. As used herein, "fibrous" includes one or more fibers that is entwined with itself, multiple fibers in a woven or non-woven mesh, and sponge like devices. The matrix should be a pliable, non-toxic, injectable porous template for vascular ingrowth. The pores should allow vascular ingrowth and the injection of cells in a desired density and region(s) of the matrix without damage to the cells. These are generally interconnected pores in the range of
between approximately 100 and 300 microns. The matrix should be shaped to maximize surface area, to allow adequate diffusion of nutrients and growth factors to the cells and to allow the ingrowth of new blood vessels and
connective tissue. The overall, or external, matrix configuration is dependent on the tissue which is to reconstructed or augmented. The shape can also be obtained using struts, as described below, to impart resistance to mechanical forces and thereby yield the desired shape. Examples include heart valve "leaflets" and tubes. The term "bioerodible", or "biodegradable", as used herein refers to materials which are enzymatically or chemically degraded in vivo into simpler chemical species. Either natural or synthetic polymers can be used to form the matrix, although synthetic biodegradable polymers are preferred for reproducibility and controlled release kinetics. Synthetic polymers that can be used include bioerodible polymers such as poly(lactide) (PLA), poly(glycolic acid) (PGA), poly(lactide-co-glycolide) (PLGA), poly(caprolactone), polycarbonates, polyamides, polyanhydrides, polyamino acids, polyortho esters, polyacetals, polycyanoacrylates and degradable polyurethanes, and non-erodible polymers such as polyacrylates, ethylene-vinyl acetate polymers and other acyl substituted cellulose acetates and derivatives thereof, non-erodible polyurethanes, polystyrenes, polyvinyl chloride, polyvinyl fluoride, poly(vinyl
imidazole), chlorosulphonated polyolifins, polyethylene oxide, polyvinyl alcohol, teflon.RTM., and nylon. Although non-degradable materials can be used to form the matrix or a portion of the matrix, they are not preferred. The preferred non-degradable material for implantation of a matrix which is prevascularized prior to implantation of dissociated cells is a polyvinyl alcohol sponge, or alkylation, and acylation derivatives thereof, including esters. In Example for they show that their invention can be used to determine if new vascularized bone could be engineered by transplantation of osteoblast around existing vascular pedicle using biodegradable polymers as cell delivery devices, to be used to reconstruct weight bearing bony defects.

Vacanti teaches what is set forth above but is not explicitly suggest the curing method steps nor the removing of inclusions. However a person having ordinary skill in the art at the time the invention was made would have found it obvious to have employed these steps as they are usually routine in chemical preparations and do not alter the final product.

Claims 1-49 meet the criteria set out in PCT Article 33(4), and thus meet industrial applicability because the subject matter claimed can be made or used in industry.